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TITLE: Effect of Repeated Caffeine Ingestion on Repeated Exhaustive Exercise Endurance

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ABSTRACT: Caffeine is known to prolong exercise times during a single bout of exhaustive exercise yet the effect on performance with repeated dosing of the drug has not been determined. Thus the purpose of this study was to examine the **effect of repeated** doses of caffeine on exercise performance. Nine male caffeine users performed exercise rides (ER) to exhaustion at 80% after ingesting a placebo, 5 mg/kg of caffeine or 2.5 mg/kg of caffeine one hour before the ER. Two ERs were performed weekly on the same day once in the morning (AM) and five hours later in the afternoon (PM). There were 4 treatments containing either caffeine or placebo (a dietary fibre) i.e., trial A representing 5 mg/kg caffeine in the AM and 2.5 mg/kg caffeine in the PM; trial B which was placebo in both AM and PM; trial C representing 5 mg/kg caffeine in the AM and placebo in the PM; and trial D representing a placebo in the AM and 5 mg/kg caffeine in the PM. The order of the treatment trials was double-blind and randomized. Caffeine ingestion significantly increased exercise time to exhaustion in the AM (trial A 24.9 ± 10.2 min and trial C 21.8 ± 4.9 versus trial B 18.0 ± 6.4 min and D 17.7 ± 4.3 min). This effect was maintained in the PM and greater than placebo (B 18.3 ± 4.8 min) regardless of whether redosing (trial A 21.5 ± 8.6 min) or placebo (trial C 21.0 ± 6.8) followed the initial morning dose. Caffeine dosing in the PM (trial D 22.4 ± 7.2 min) also increased ER following placebo trial D in the AM. It wa

Il y a un résumé français ici.

IDENTIFIERS: time to exhaustion;ergogenic aids;re-dosing;carry-over effects;repeated exercise

REPORT NUMBER: DRDC-TORONTO-SL-2002-194; Scientific Literature | **REPORT DATE:** 01 Jan 2003 | **NUMBER OF PAGES :** 8

Reprints: Medicine and Science in Sports and Excersise, vol 35, no 8, 2003, p 1348-1354

DRDKIM N°: CA025730 | **CANDIS N°:** 523441 | **Format(s):** CD ROM

Date modified: 2005-04-05

Effect of Repeated Caffeine Ingestion on Repeated Exhaustive Exercise Endurance

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ABSTRACT

BELL, D. G., and T. M. MCLELLAN. Effect of Repeated Caffeine Ingestion on Repeated Exhaustive Exercise Endurance. *Med. Sci. Sports Exerc.*, Vol. 35, No. 8, pp. 1348–1354, 2003. **Purpose:** The purpose of this study was to examine the effect of repeated doses of caffeine on repeated exercise endurance. **Methods:** Nine male caffeine users performed exercise rides (ER) to exhaustion at 80% VO_{2max} after ingesting a placebo, 5 mg·kg^{-1} of caffeine, or 2.5 mg·kg^{-1} of caffeine 1 h before the ER. Two ER were performed weekly on the same day once in the morning (AM) and 5 h later in the afternoon (PM). There were four treatments containing either caffeine or placebo, i.e., trial A representing 5-mg·kg^{-1} caffeine in the AM and 2.5-mg·kg^{-1} caffeine in the PM; trial B, which was placebo in both AM and PM; trial C representing 5-mg·kg^{-1} caffeine in the AM and placebo in the PM; and trial D representing a placebo in the AM and 5-mg·kg^{-1} caffeine in the PM. The order of the treatment trials was double blind and randomized. **Results:** Caffeine ingestion significantly increased exercise time to exhaustion in the AM (trial A 24.9 ± 10.2 min and trial C 21.8 ± 4.9 vs trial B 18.0 ± 6.4 min and D 17.7 ± 4.3 min). This effect was maintained in the PM and greater than placebo (B 18.3 ± 4.8 min) regardless of whether redosing (trial A 21.5 ± 8.6 min) or placebo (trial C 21.0 ± 6.8) followed the initial morning dose. Caffeine dosing in the PM (trial D 22.4 ± 7.2 min) also increased ER after placebo trial D in the AM. **Conclusions:** It was concluded that redosing with caffeine after exhaustive exercise in the AM was not necessary to maintain the ergogenic effect of the drug during subsequent exercise 6 h later. **Key Words:** TIME TO EXHAUSTION, ERGOGENIC AIDS, CARRY-OVER EFFECTS, CYCLING

The ergogenic effects of caffeine ingestion during submaximal exercise are well documented in a number of recent reviews (7,12,22). Most studies have looked at exercise endurance approximately 1 h after caffeine ingestion when plasma concentrations of the drug are close to maximal (4,13,14,23–25,27). Recently, we reported that both the magnitude and duration of the ergogenic effect that followed a 5-mg·kg^{-1} dose of caffeine differed between users and nonusers of the drug (1). For caffeine users, exercise endurance was improved approximately 20% one and three hours after caffeine ingestion, but performance had returned to placebo levels 6 h later. In contrast, endurance was increased by 30% for nonusers of the drug for up to 6 h after caffeine ingestion. In that study, plasma caffeine concentrations decreased from 36 μmol·L^{-1} 1 h after caffeine ingestion to 27 μmol·L^{-1} 6 h later for users of the drug (1), implying that this lower concentration was insufficient to induce the ergogenic effect. Thus, the focus of the present study was to examine whether restoring plasma concentrations to these higher values would again be associated with an improvement in exercise endurance. For athletes and the military, it would seem critical to know not only when a particular ergogenic aid should be taken to produce its effect but also when and whether further dosing should be used to maintain the ergogenic benefit. It is not uncommon for athletic events or military operations to involve repeated bouts of exercise or work throughout the day. Any strategy that can be adopted to enhance the performance of the athlete or soldier over these periods would be advantageous.

To our knowledge, the evaluation of exercise endurance during the morning and afternoon after redosing of caffeine has not been studied. Others have examined the effects of repeated dosing of caffeine throughout a prolonged exercise task on the performance of a subsequent time trial or exercise test to exhaustion (5,8). For example, Cox et al. (5) reported a small 3% improvement in time trial performance that followed 2 h of exercise at 70% $\dot{V}O_{2max}$ for trained cyclists regardless of whether 6 mg·kg^{-1} of caffeine was ingested in a single dose before or divided into six equal doses and administered at 20-min intervals throughout the 2 h of exercise. In contrast, Falk et al. (8) observed that cycle time to exhaustion at 90% $\dot{V}O_{2max}$ was not improved after an 8-h, 40-km march when blood caffeine levels were maintained at high levels with an initial 5-mg·kg^{-1} dose of the drug that was supplemented after 3 and 5 h of marching with additional 2.5-mg·kg^{-1} caffeine doses. However, neither of these studies examined repeated exercise tests that were separated by a period of recovery.

It was the purpose of this study, therefore, to determine whether redosing with caffeine would be an efficacious strategy to maintain the ergogenic effects of the drug during repeated exercise bouts i.e., one in the morning and another

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Submitted for publication December 2002.
Accepted for publication April 2003.

0195-9131/03/3508-1348
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DOI: 10.1249/01.MSS.0000079071.92647.F2

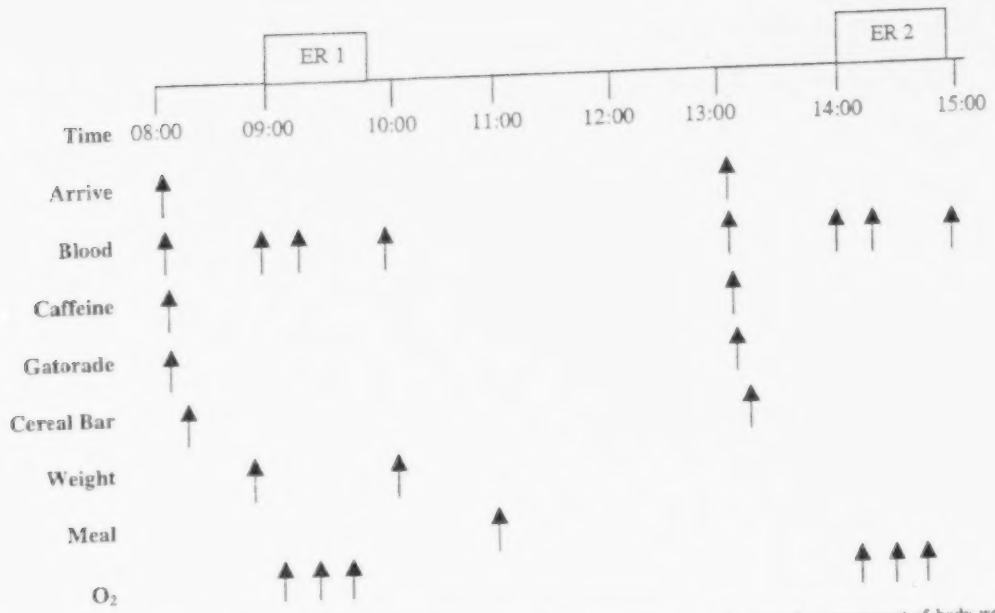

FIGURE 1—Time line for arriving, blood sampling, delivery of caffeine, GATORADE, cereal bar, food, and measurement of body weight and oxygen consumption (O_2) during the treatment trials.

in the afternoon. Thus, one exhaustive exercise bout at 80% VO_{2max} was performed 1 h after an initial 5-mg·kg^{-1} dose of caffeine was ingested in the morning, and the second was performed 1 h after an additional 2.5-mg·kg^{-1} maintenance dose was administered in the afternoon. The 2.5-mg·kg^{-1} dose was administered 5 h after the initial dose was consumed. We hypothesized that this dosing regimen would maintain the ergogenic effect of the drug during exercise performed in the afternoon at a similar level to the effect observed during the morning exercise.

METHODS

Subjects. Nine healthy males subjects with mean ± SD values for age 33 ± 7, height 178 ± 9 cm, and body mass 86.0 ± 9.0 kg participated in this study. All subjects were recreational cyclists and had a cycle ergometer aerobic power (VO_{2max}) of 52 ± 9 mg·kg^{-1}·min^{-1}. They were all caffeine users (ingesting ≥ 300 mg caffeine·d^{-1}) as categorized by their response to a questionnaire on caffeine use administered at the beginning of the study. Caffeine was predominantly ingested in the form of coffee; however, other caffeine products were also ingested, i.e., tea, colas, and chocolate candy bars. The subjects were fully informed of the details, discomforts, and risks associated with the experimental protocol, and written informed consent was obtained. The subjects were asked to refrain from heavy exercise and alcohol for 24 h, and to refrain from caffeine or products containing caffeine for 12 h before each trial. This study was granted approval by the Human Ethics Committee of the Defense R&D Canada–Toronto.

Procedures. The subjects visited the laboratory on seven occasions. During the initial visit, subjects were medically screened and had their VO_{2max} determined on an electrically braked cycle ergometer (Ergometrics 800, SensorMedics, Yorba Linda, CA). The subjects began pedaling at a power output of 100 W, and this was increased 50 W every 4 min for four submaximal power outputs. Thereafter, the work rate was increased 30 W every minute until exhaustion. Open-circuit spirometry was used to determine oxygen consumption (VO_2) every 30 s, and the highest value obtained was defined as the VO_{2max}. Heart rate (HR) was monitored continuously using a transmitter/telemetry unit (Vantage XL Polar System, Port Washington, NY). The relationship between VO_2 and power output was derived from this test and from that relationship the power output equivalent to 50 and 80% VO_{2max} was used during the subsequent trials on the same ergometer.

During visit 2, subjects were asked to record all food and caffeinated beverages consumed for the previous 2-d period. Subjects were then instructed to attempt to replicate this diet for the 2-d period before each of the remaining trials. During the next six visits, which were scheduled weekly, the subject performed the exhaustion ride (ER) twice daily during the visit, once in the morning (AM) and 5 h later in the afternoon (PM). The ER consisted of two phases. The first phase involved 5 min of cycling at 50% VO_{2max} with a pedal frequency that was self-selected between 60 and 100 rev·min^{-1}. Immediately thereafter, the second phase began, which consisted of a ride to exhaustion at 80% VO_{2max} at the same pedaling frequency. Also during these visits, meal and caffeine beverage consumption of the previous 2 d was recorded.

Visits 2 and 3 were familiarizations to the treatment procedures as depicted in Figure 1 and explained below. During the familiarization trials, no treatment capsules were

ingested. During the treatment trials, there were four orders for the presentation of the treatment capsules containing caffeine and placebo (a dietary fiber), i.e., trial A consisted of 5-mg·kg^{-1} caffeine in the AM and 2.5-mg·kg^{-1} caffeine in the PM; trial B was placebo in both AM and PM; trial C consisted of 5-mg·kg^{-1} caffeine in the AM and placebo in the PM; and trial D consisted of a placebo in the AM and 5-mg·kg^{-1} caffeine in the PM. Each subject acted as their own control and underwent all trials. Treatment trials were double blind and randomized. Drug and placebo were ingested in opaque gelatin capsules.

Immediately after arriving, a catheter was inserted into an antecubital vein and an initial blood sample was taken. Additional blood samples were taken just before the ER, after 10 min of exercise at 80% VO_{2max}, and at exhaustion. After the initial blood sample either caffeine or placebo capsules were ingested with a volume of GATORADE® equivalent to 5 mg·kg^{-1}. Although the use of GATORADE® to ensure hydration before beginning the exercise trials may have represented a confounding factor with the ingestion of caffeine (17), this procedure was followed to be consistent with our previous work (1). Fifteen minutes later, the subject ate a cereal bar. Forty-five minutes later and just before the first ER, the subject's nude weight was measured. The subject then dressed and performed the first ER after which they were again weighed and given a volume of GATORADE equivalent to the sweat lost. Approximately 1 h after completion of the first ER, the subject was given a light breakfast. Except for obtaining nude weights and providing this meal, these same procedures were followed for the second ER and commenced 5 h after the initial dose.

During the ER, open-circuit spirometry was used to determine VO_2 during the first 5 min of warm-up and 5 min of 80% VO_{2max}, at 15 min of 80% VO_{2max}, and at 15-min intervals thereafter. A whole-body rating of perceived exertion (RPE) using the Borg scale (2) and HR were recorded every 5 min. Subjects performed the ER dressed in their normal cycling gear. The ER was conducted in a room that was controlled at 20–22°C.

Measurements. For the treatment trials, plasma was assayed for free fatty acid (FFA, NEFA C Kit, Waco, TX) and for caffeine concentration using gas chromatograph-mass spectrometry electron impact single ion monitoring (model MSD 5970a Hewlett Packard, Palo Alto, CA). Another aliquot of each blood sample was immediately deproteinized and subsequently assayed for glucose (GOD-PAP, Roche Diagnostics, Germany) and lactate (20).

Statistics. A repeated measures ANOVA with two within (time of day × trial) factors was used to compare the times to exhaustion during ER. For all other variables, a repeated measures ANOVA with three within (time of day × trial × time during exercise) factors was used to compare the dependent measures. To correct for the violation of the sphericity assumption with the repeated factors a Huynh-Feldt correction was applied to the F-ratio. When the ANOVA yielded a significant F-ratio, a *post hoc* comparison of means was done with a means comparison contrast technique (11). Statistical significance was accepted at the $P < 0.05$ level.

RESULTS

Time to exhaustion. Figure 2 presents time to exhaustion for the ER. Caffeine ingestion significantly increased exercise time to exhaustion compared with all of the placebo runs with the exception of the PM ride in trial C that followed caffeine ingestion in the AM. Overall caffeine ingestion in the AM increased time to exhaustion by 31.3 ± 18% compared with placebo in the AM. This ergogenic effect was not different between trials A and C although the response appeared larger for the former trial. Redosing with caffeine in the PM preserved the ergogenic effect relative to placebo (PM trial B) and maintained the ergogenic effect observed earlier that same day during trial A. However, redosing with caffeine in the PM was not necessary to maintain the ergogenic effect that followed caffeine ingestion in the morning during trial C. Finally, exhaustive exercise performed in the AM did not prevent the ergogenic effect of caffeine to be observed during subsequent exercise in the PM.

Oxygen consumption ($\dot{V}O_2$). Table 1 shows that during the warm-up phase at 50% VO_{2max} caffeine ingestion

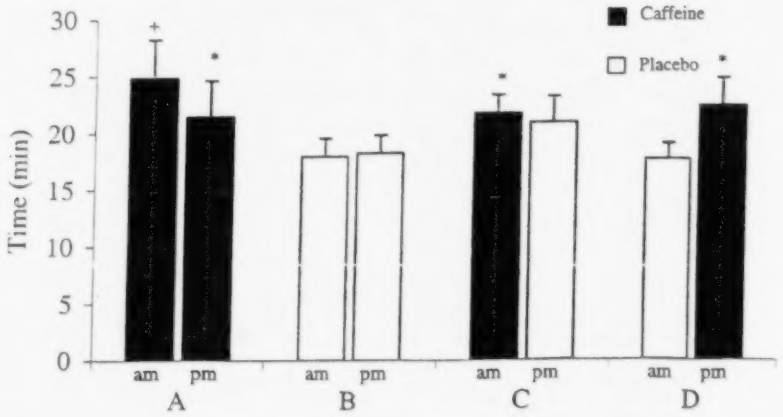

FIGURE 2—Time to exhaustion at 80% VO_{2max} after caffeine or placebo ingestion. * Significantly different from B (AM, PM) and D (AM); + significantly different from all placebo trials.

did not affect VO_2, whereas there was a small but consistent and significant increase in VO_2 after caffeine ingestion during exercise at 80% VO_{2max}. There was also a main effect of time with VO_2 increasing from 3.43 ± 0.57 $L \cdot min^{-1}$ at 5 min to 3.60 ± 0.57 $L \cdot min^{-1}$ after 15 min of exercise at 80% VO_{2max}.

Respiratory exchange ratio (RER). After caffeine ingestion, the RER during exercise at 50% (1.01 ± 0.04) and 80% (1.09 ± 0.05) VO_{2max} was not different from placebo (1.00 ± 0.04 and 1.11 ± 0.05 at 50% and 80% VO_{2max}, respectively). During exercise at 80% VO_{2max}, there was, however, a significant decrease in RER as exercise time increased from 1.13 ± 0.04 at 5 min to 1.07 ± 0.04 at 15 min.

Heart rate (HR). The HR response during exercise at 50% VO_{2max} was similar for the caffeine (123 ± 14 $beats \cdot min^{-1}$) and placebo (123 ± 13 $beats \cdot min^{-1}$) trials. There was, however, a time-of-day effect with higher HR in the afternoon (127 ± 15 $beats \cdot min^{-1}$) compared with the morning (120 ± 12 $beats \cdot min^{-1}$).

During exercise at 80% VO_{2max}, HR increased from 159 ± 13 $beats \cdot min^{-1}$ at 5 min to 168 ± 12 $beats \cdot min^{-1}$ at 15 min. The HR response was similar for the caffeine (165 ± 13 $beats \cdot min^{-1}$) and placebo (163 ± 13 $beats \cdot min^{-1}$) trials. No time-of-day effect was noted for the 80% phase of the ER (163 ± 12 $beats \cdot min^{-1}$ for AM vs 164 ± 14 $beats \cdot min^{-1}$ for PM).

Rating of perceived exertion (RPE). Caffeine had no effect on RPE during exercise at 50% VO_{2max} (8.8 ± 1.2 for caffeine vs 8.6 ± 1.1 for placebo, Table 2). However, during exercise at 80% VO_{2max}, caffeine reduced RPE (14.7 ± 2.2) compared with placebo (15.6 ± 2.3). Also during this phase of the ER, RPE increased from 13.0 ± 1.4 at 5 min to 17.0 ± 1.6 at 15 min. Further, RPE was lower during the AM trials (14.7 ± 2.3) compared with the PM (15.5 ± 2.2).

Lactate. Before exercise lactate was similar after caffeine (1.04 ± 0.21 $mmol \cdot L^{-1}$) or placebo ingestion (0.95 ± 0.24 $mmol \cdot L^{-1}$). However, during exercise lactate was significantly increased by caffeine ingestion (6.87 ± 1.59 $mmol \cdot L^{-1}$) compared with placebo (6.30 ± 1.60 $mmol \cdot L^{-1}$). Further, there was a main effect of time as lactate increased from 6.16 ± 1.38 $mmol \cdot L^{-1}$ after 10 min of exercise at 80% VO_{2max} to 7.01 ± 1.71 $mmol \cdot L^{-1}$ at exhaustion.

TABLE 1. Mean ± SD oxygen consumption (VO_2 $L \cdot min^{-1}$) during exercise after caffeine or placebo ingestion.

	A	B	C	D
AM	Caffeine	Placebo	Caffeine	Placebo
5 min 50%	2.03 ± 0.29	1.97 ± 0.33	2.07 ± 0.31	1.99 ± 0.24
5 min 80%	3.41* ± 0.58	3.39 ± 0.62	3.42* ± 0.61	3.40 ± 0.62
15 min 80%†	3.62* ± 0.62	3.50 ± 0.59	3.62* ± 0.60	3.54 ± 0.53
PM	Caffeine	Placebo	Placebo	Caffeine
5 min 50%	2.03 ± 0.24	2.10 ± 0.24	2.04 ± 0.34	2.09 ± 0.33
5 min 80%	3.50* ± 0.61	3.40 ± 0.58	3.39 ± 0.57	3.50* ± 0.61
15 min 80%†	3.63* ± 0.59	3.58 ± 0.63	3.58 ± 0.64	3.69* ± 0.60

* Caffeine > placebo.
† VO_2 increased with exercise time.

TABLE 2. Mean ± SD rating of perceived exertion (RPE) during exercise after caffeine or placebo ingestion.

	A	B	C	D
AM#	Caffeine	Placebo	Caffeine	Placebo
5 min 50%	8.6 ± 1.2	8.1 ± 0.9	8.7 ± 0.8	8.8 ± 1.1
5 min 80%	12.4* ± 1.4	12.8 ± 1.1	12.7* ± 1.6	12.7 ± 1.2
10 min 80%	14.3* ± 1.4	15.4 ± 2.1	14.3* ± 1.8	14.9 ± 1.5
15 min 80%†	15.8* ± 2.0	17.7 ± 1.1	15.8* ± 1.7	17.5 ± 0.9
PM	Caffeine	Placebo	Placebo	Caffeine
5 min 50%	8.6 ± 1.3	8.6 ± 0.9	9.0 ± 1.3	9.2 ± 1.5
5 min 80%	13.1* ± 1.2	14.0 ± 1.7	13.6 ± 1.1	13.1* ± 1.3
10 min 80%	15.9* ± 1.6	16.7 ± 1.6	15.7 ± 1.5	14.9* ± 1.7
15 min 80%†	17.1* ± 1.5	18.2 ± 1.2	17.4 ± 1.2	16.6* ± 1.8

* Caffeine < placebo.
† As exercise time increased so did RPE.
# Morning RPE < afternoon RPE.

Free fatty acid (FFA). Caffeine had no effect on FFA levels before or during exercise. There was, however, a time-of-day effect. FFA levels observed in the afternoon for both the pre (0.276 ± 0.125 $mmol \cdot L^{-1}$) and exercise phase (0.316 ± 0.142 $mmol \cdot L^{-1}$) were higher than in the morning for the pre (0.147 ± 0.120 $mmol \cdot L^{-1}$) and exercise phase (0.177 ± 0.121 $mmol \cdot L^{-1}$). Also, FFA was greater at the end of exercise (0.278 ± 0.163 $mmol \cdot L^{-1}$) compared with values measured during exercise (0.216 ± 0.127 $mmol \cdot L^{-1}$).

Glucose. Caffeine elevated glucose levels both before (3.7 ± 0.6 $mmol \cdot L^{-1}$) and during exercise (3.7 ± 1.1 $mmol \cdot L^{-1}$) compared with the respective values of 3.4 ± 0.6 $mmol \cdot L^{-1}$ and 3.3 ± 0.8 $mmol \cdot L^{-1}$ for placebo. Also, glucose was elevated at the end of exercise (3.8 ± 1.1 $mmol \cdot L^{-1}$) compared with values measured after 10 min of exercise (3.1 ± 0.5 $mmol \cdot L^{-1}$) at 80% VO_{2max}.

Caffeine concentration. Figure 3 shows the concentration of caffeine in the plasma after 10 min of riding at 80%VO_{2max} after caffeine or placebo ingestion. Redosing with 2.5 $mg \cdot kg^{-1}$ of caffeine during trial A in the PM produced similar caffeine concentrations to those observed 1 h after the initial 5-$mg \cdot kg^{-1}$ dose in the AM. When the 5-$mg \cdot kg^{-1}$ dose of caffeine was ingested in the PM (trial D), plasma concentrations were lower than when the same dose was ingested in the AM. Caffeine concentrations during the placebo trail in the PM (trial C) were significantly reduced compared with levels obtained after the 5-$mg \cdot kg^{-1}$ dose in the AM (trial C), but they were still significantly increased compared with the other placebo trials. Also, caffeine concentrations during this PM trial (C) were not different than those levels obtained when the 5-$mg \cdot kg^{-1}$ caffeine dose was ingested in the PM (trial D).

DISCUSSION

To our knowledge, the present study is the first to examine the ergogenic effects of caffeine during repeated bouts of exhaustive exercise performed on the same day. The impetus for this work evolved from an earlier report that revealed a return to placebo level endurance 6 h after a 5-$mg \cdot kg^{-1}$ dose of caffeine for regular users of the caffeine (1) and our interest to explore the application of using caffeine for a

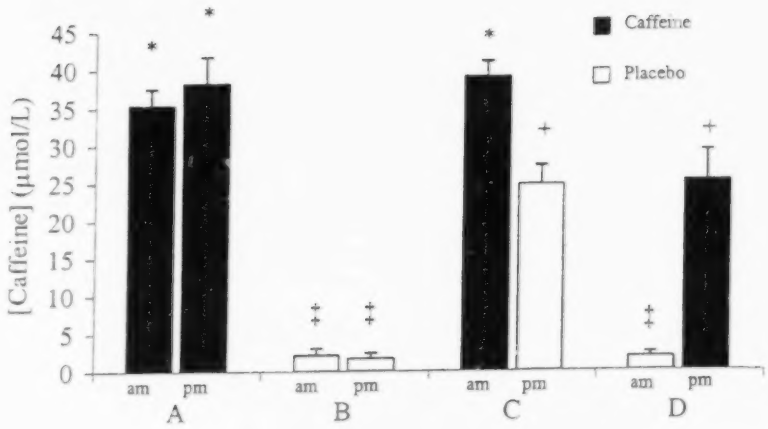

FIGURE 3—Caffeine concentration in the blood after 10 min of exercise at 80% VO_{2max}. *+‡ Trials with the same symbol are not different from each other, whereas different symbols indicate a significant difference.

military or athletic scenario that involved repeated bouts of exhaustive exercise throughout the day. We hypothesized that restoring blood caffeine concentrations to the peak levels observed 1–2 h after an initial dose would maintain the ergogenic effects regardless of whether single or multiple exhaustive exercise bouts were performed. Our new findings show that although similar high blood concentrations of caffeine maintain the ergogenic effects of the drug during repeated exhaustive exercise (trial A), a lower blood concentration before the second ER was not associated with a loss of the ergogenic effect of the drug (trial C). Our data also show that the ergogenic effect that follows caffeine ingestion can occur at lower blood concentrations during a subsequent bout of exhaustive exercise in the afternoon (trial D).

Caffeine acts as an A_1 and A_{2a} adenosine receptor antagonist (10), and regular consumption of caffeine is associated with an up-regulation of the number of these adenosine receptors in the vascular and neural tissues of the brain (10,16,21). In our previous work which involved a single exhaustive exercise bout at 80% VO_{2max}, a decrease in the blood concentration of caffeine from 36 $\mu mol \cdot L^{-1}$ 1 h after drug ingestion to 27 $\mu mol \cdot L^{-1}$ 6 h later was associated with a loss of the ergogenic effect of caffeine on exercise endurance for regular users of caffeine (1). These findings implied that a blood concentration of caffeine in excess of 27 $\mu mol \cdot L^{-1}$ was necessary to exert an ergogenic effect for users of the drug. However, in the present study that involved two exhaustive exercise bouts at 80% VO_{2max}, a similar decrease in the blood concentration of caffeine (see Fig. 3) was not associated with a return of performance to placebo levels. Because blood concentrations were similar over the 6-h period after the ingestion of the initial 5-$mg \cdot kg^{-1}$ dose of caffeine in the two studies, the first exhaustive exercise bout (used in the present investigation) does not appear to have influenced clearance rates of the drug. Also our subjects did not differ with respect to their history of caffeine use, training status, fitness, or age. In fact, several of the subjects participated in our previous study. Thus, we are left to speculate that there was a down-regulation of the number of adenosine receptors or a change in receptor affinity that followed the first exhaustive exercise session and increased the sensitivity to caffeine for these users of the drug. In other words, their response during trial C in the afternoon became similar to the response observed for nonusers of the drug in our previous study (1). Further, a down-regulation of receptor number and increased sensitivity to caffeine would account for the ergogenic effect observed during the afternoon of trial D at lower circulating concentrations of the drug and the nonsignificant decrease in endurance ($P < 0.08$) during the afternoon of trial A where blood concentrations were maintained at high levels. We are unaware of any studies that have examined the effects of an acute exercise bout on subsequent caffeine sensitivity and adenosine receptors. However, a single bout of exercise has been reported to alter the adenosine receptor-mediated response to insulin in the soleus muscle of the rat (19) and the postexercise vascular responses in the rabbit hindlimb (15). Thus, it is possible that adenosine receptors in the muscles and the brain and their sensitivity to caffeine could be altered for several hours after a single exhaustive exercise bout.

Few studies have examined the effects of a redosing regimen of caffeine on exercise endurance. Falk et al. (8) loaded subjects with an initial 5-$mg \cdot kg^{-1}$ dose of caffeine before initiating a 40-km march and then followed this with 2.5-$mg \cdot kg^{-1}$ doses after 3 and 5 h of the march. At the completion of the march 8 h later, cycle time to exhaustion at 90% VO_{2max} was determined. Inclement weather prevented a repeated-measures design from being implemented, and thus a between-group (drug vs placebo) difference of 40% in exercise times to exhaustion failed to attain significance. Actual cycle times were 6.1 and 4.3 min for the caffeine and placebo groups, respectively. Those that did receive the caffeine, however, reported a lower rating of perceived exertion at the end of the march and had higher blood lactate levels after the ride to exhaustion.

Cox et al. (5) compared the effects of a single 6-$mg \cdot kg^{-1}$ dose of caffeine given before 120 min of exercise at 70% VO_{2max} with six repeated 1-$mg \cdot kg^{-1}$ doses of the drug

given at 20-min intervals throughout the exercise on time trial performance at the end of the 2 h of cycling. These investigators also examined the benefits of ingesting a 5-mg·kg^{-1} dose of a caffeinated cola during the last 20-min of exercise at 70% VO_{2max} and during the initial stages of the time trial on the performance of the time trial. All caffeine-dosing strategies produced the same 3% improvement in time trial performance compared with placebo despite the fact that blood caffeine concentrations were significantly lower before and at the end of the time trial with the treatment involving the caffeinated beverage (5).

These latter findings are consistent with the ergogenic effect that has been observed during a time-trial effort lasting approximately 1 h after the ingestion of a carbohydrate and electrolyte solution that contained various doses of caffeine from 2 to 4.5 mg·kg^{-1} (18). In this study, approximately 60% of the total dose of caffeine was ingested 75 min before the start of the time trial during a 20-min warm-up period of light exercise, whereas the remaining 40% of the dose was divided into two equal portions and administered after one-third and two-thirds of the total work output was accomplished during the time trial (18). Performance of the time trial was increased significantly from 3% to 6% with the varying doses of caffeine compared with placebo. It is interesting that all of these studies (1,5,8) examined the ergogenic effect of caffeine during a performance test that was preceded by submaximal exercise. Thus, it is possible that the prior exercise ultimately affected the subjects' sensitivity to the circulating concentrations of caffeine.

It is also of interest that caffeine concentrations after the 5-mg·kg^{-1} dose administered in the afternoon were lower than when the same dose was administered in the morning (compare trial D in the PM with trials A and C in the AM in Fig. 3). Temporal changes in the absorption, distribution, metabolism, and elimination of caffeine can be effected by circadian or biological rhythms (3). Shorter times to maximum plasma concentrations of drugs have been found in the morning because of circadian effects on gastrointestinal blood flow (3). It is also possible that the meal given a few hours before the caffeine ingestion in the afternoon could have delayed the absorption of the drug (9). We do not know whether higher concentrations would have been observed had subjects been in a greater postprandial state. Equally, we do not know whether exercise endurance would have been adversely or positively affected had higher blood concentration been observed during the afternoon of trial D. In the present study, it may have been fortuitous that the lower concentrations of caffeine after the 5-mg·kg^{-1} dose of the drug in the PM produced the same ergogenic effect that followed ingestion of caffeine in the AM.

What are the implications of our findings for the athlete or military personnel involved with repeated exercise bouts at different times of the day? First, performing exhaustive exercise for 20–30 min in the morning does not adversely affect the endurance during the same event or task 5 h later in the afternoon. Thus, scheduling of athletic events or military operations could involve repeated exhaustive exercise bouts separated by at least 5 h of recovery. Second, the ingestion of a second smaller dose of caffeine before the performance of a second exhaustive exercise bout is not necessary to maintain the 20–30% improvement in time to exhaustion that follows ingestion of a higher dose of the drug in the morning. In fact, this additional dose of the drug has a tendency to adversely affect endurance. We are speculating that the initial exercise bout alters one's sensitivity to circulating levels of caffeine such that the ergogenic effect of the drug on a successive bout of exercise is evident much longer than was previously reported for a single bout of exercise (1). We do not know for how long this altered sensitivity might last and whether this would be different between users and nonusers of the drug. These are questions that require further investigation. However, based on our previous findings (1) we would still advocate redosing with caffeine 5 h after an initial 5-mg·kg^{-1} dose if prior exercise did not occur.

The cardiorespiratory, RPE, and metabolic responses seen in the present study are similar to those reported previously during exercise that followed caffeine ingestion, generally either no change or a slight increase in VO_2 (1,4,25), HR (1,13,26), glucose (1,4,14), and FFA, or (1,14,25) no change in RER (1,14,26), a decreased RPE (1,4,6,8), and an increased blood lactate (1,8,14). Similarly, the 30% improvement in time to exhaustion during the morning exercise trials in the present study is comparable to improvements noted by others after the ingestion of an equivalent dose of caffeine 1 h before exercise (1,4,13). The repeatability of this ergogenic effect was quite variable, however, with a larger 38% mean improvement noted in the morning for trial A that was not significantly different than the 23% increase noted after trial C. Individual improvement relative to the placebo trials varied from −6% to +76% for trial A and from −2% to 46% for trial C. For some subjects, the changes relative to the placebo trials were quite variable, showing a 65–75% improvement during one trial that was reduced to 20–30% during a subsequent trial. Our subjects were not elite athletes, and although we attempted to control the influence of diet, rest, prior exercise, and over-the-counter medications, some of these factors may have affected the subjects' response to the ingested caffeine. The reader should be aware of this variability, therefore, if they are attempting to use caffeine in a setting that prevents the control of many extraneous factors that alone or in combination could influence exhaustive exercise endurance.

In conclusion, this study has found that the ergogenic effect during exhaustive exercise at 80% VO_{2max} that follows a 5-mg·kg^{-1} dose of caffeine is maintained 5 h later during a subsequent exercise challenge. Thus, the need to ingest a smaller additional dose of the drug to maintain blood concentrations at high levels does not appear necessary to enhance exercise endurance. In fact, a lower blood concentration of caffeine in the afternoon is associated with the same ergogenic effect that is observed with higher concentrations of the drug in the morning. Finally, the study has shown that there do not appear to be any negative carry-over effects associated with the performance of ex-

haustive exercise at 80% VO_{2max} in the morning on subsequent exercise in the afternoon.

The authors are grateful to Mrs. Ingrid Smith, who spent many hours conducting the trials, gathering the data, and analyzing blood samples. Also we wish to thank Mr. Gary Seabrook and Ms. Deanna Lindsay for analyzing the blood samples for caffeine content. Further, we would like to acknowledge Mr. Bill Phillips of Bulk Pharmaceutical Incorporated for providing the caffeine.

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